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The beneficial effects of lipid-lowering drugs beyond lipid-lowering effects: A comparative study with pravastatin, atorvastatin, and fenofibrate in patients with type IIa and type IIb hyperlipidemia

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Abstract

Hyperlipidemia is an important risk factor for atherosclerosis. Hemorheological factors contribute to morbidity and mortality in patients with dyslipidemia. We evaluated the effects of 3 antihyperlipidemic drugs (pravastatin, atorvastatin, and fenofibrate), which have different mechanisms of action and different patterns of action on lipid profiles, on erythrocyte deformability and fibrinogen levels in patients with type IIa and type IIb hyperlipidemia. Twenty-one patients (4 men and 17 women) with type IIa and IIb hyperlipidemia were randomized to 3 drugs (pravastatin 20 mg/d, atorvastatin 10 mg/d, fenofibrate 250 mg/d) for 8 weeks. Plasma glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) analysis were performed on a BM-Hitachi 747-200 autoanalyzer (Hitachi-Roche, Tokyo, Japan). Fibrinogen analysis was performed according to Clauss method. Erythrocyte deformability was assessed with cell transit analysis device.There was no significant difference in body mass index, lipid profile, fibrinogen level, and erythrocyte deformability index values among the groups before treatment ($P > .05$). In all groups, there were statistically significant reductions in total LDL-C levels ($P < .05$). The triglyceride levels were significantly reduced in the atorvastatin and fenofibrate groups ($P < .05$), but not in the pravastatin group ($P > .05$). There was no significant change in HDL-C levels during the treatment with statins ($P > .05$), but there was a significant increase in the fenofibrate group ($P < .05$). Mean erythrocyte deformability index was improved in all the groups ($P < .05$). There was no significant change in fibrinogen levels during the treatment of pravastatin and atorvastatin ($P > .05$), but in fenofibrate group, fibrinogen levels were significantly decreased ($P < .05$).

The 3 groups of antihyperlipidemic drugs have beneficial effects on the erythrocyte deformability index. Only fenofibrate has significant beneficial effects on the fibrinogen levels.

1. Introduction

Hyperlipidemia is an important risk factor for atherosclerosis [1]. Epidemiological and clinical studies indicate that hyperlipidemia is associated with alterations in hemostatic and hemorheological factors [2,3]. Hemorheological factors such as blood viscosity, platelet activation state, and erythrocyte deformability contribute to morbidity and mortality in patients with dyslipidemia [4-7]. Erythrocyte deformation is an important regulatory factor of microcirculation [8]. Erythrocyte deformability deteriorates in patients with hyperlipidemia [3,9]. There are some reports that antihyperlipidemic treatment may improve erythrocyte deformability [9-13]. Although the effects of antihyperlipidemic drugs are well known, there is no concensus about the effects of these drugs on hemorheological parameters [14-16]. In one study, pravastatin was reported to significantly decrease plasma fibrinogen levels and plasma viscosity, but did not significantly change whole blood rheology in patients with familial hypercholesterolemia [9].

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In another study, lovastatin treatment decreased plasma viscosity and red cell aggregation, but did not change plasma fibrinogen level significantly [2]. Furthermore, Beigel et al [17] reported improvement in red blood cell filterability with an increase in fibrinogen levels with lovastatin treatment. As with the previous statins, there is also no consensus about the effect of atorvastatin [13,18].

The fibrate group is one of the oldest nonstatin medications for hyperlipidemia. Fibrates are normolipidemic drugs that decrease triglyceride and increase HDL concentrations in human beings. Fibrates are efficient drugs for the treatment of specific atherogenic lipid disorders, such as combined hyperlipidemia and hypoalphalipoproteinemia [19].

In this study, we compared the effects of 3 antihyperlipidemic drugs (pravastatin, atorvastatin, and fenofibrate) that have different mechanisms of action and different patterns of action on lipid profiles, on erythrocyte deformability, and on fibrinogen levels in patients with type IIa and type IIb hyperlipidemia.

2. Materials and methods

2.1. Patients

Twenty-one patients (4 men and 17 women; mean age, 51.7 ± 9.1 years) with type IIa (isolated hypercholesterolemia, LDL-C >160 mg/dL and triglycerides <200 mg/dL) and type IIb (mixed hyperlipidemia, LDL-C >160 mg/dL and triglycerides >200 mg/dL) hyperlipidemia were recruited and randomized to 3 groups. In each group, there were 7 age- and sex-matched patients. Groups A, B, and C were treated by pravastatin 20 mg/d, atorvastatin 10 mg/d, and fenofibrate 250 mg/d for 8 weeks, respectively. None of the patients had diabetes, renal failure, or myocardial infarction. Patients with endocrine, liver, hepatic, thyroid, and renal disorders, body mass index (BMI) of less than 30 kg/m^2, and alcohol abuse were excluded. Drugs with a known or potential effect on lipid levels or hemorheological parameters (β-blockers, thiazids, corticosteroids, estrogens, and aspirin) were not allowed during the study period. Informed consent was obtained from each subject before the study.

2.2. Methods

Weight and height were measured in light clothing without shoes. Body mass index was calculated as weight divided by height squared (kilograms per meter squared). The blood analysis was performed between 8:00 and 9:00 AM after 12 hours of fasting.

To maximize uniformity of diets and lifestyle habits, patients had dietary stabilization 6 weeks before the drug administration after counseling by a dietitian on the National Cholesterol Education Program Step 1 diet.

Plasma glucose, total cholesterol, triglyceride, and HDL-C, aspartate aminotransferase, alanine aminotransferase creatinine kinase, and lactate dehydrogenase levels were measured using SIGMA enzymatic kits (Sigma Diagnostics, Taufkirchen, Germany) in a BM-Hitachi 747-200 autoanalyzer (Hitachi-Roche, Tokyo, Japan). Low-density lipoprotein cholesterol was calculated by the Friedwald equation, except in patients with triglyceride levels higher than 400 mg/dL. Low-density lipoprotein cholesterol levels in patients with triglyceride levels higher than 400 mg/dL were measured using a bioMérieux Diagnostic (Lyon, France) LDL-C kit in a BM-Hitachi 747-200 autoanalyzer.

Fibrinogen analysis was performed according to the Clauss method [20].

Venous blood samples anticoagulated with heparin were analyzed to assess whole erythrocyte deformability within 30 minutes of sampling. Erythrocyte deformability was assessed by a cell transit analysis device. Erythrocyte deformability was assayed by measuring the erythrocyte filtration rate at which a 20% suspension of washed erythrocytes passed through nucleopore polycarbonate membrane with a 15-mm diameter and a pore of 5-μm filter [21-23].

Statistical tests were performed using a commercial software package (SPSS 8.0). Nonparametric tests (Mann-Whitney U test and Wilcoxon signed rank test) were used.

3. Results

3.1. Baseline parameters

In each group, there were sex- and age-matched 7 patients. As shown in the Table 1, there was no significant

Table 1
Baseline and posttreatment levels of lipid and hemorheological parameters

	Pravastatin (mean ± SE)		Atorvastatin (mean ± SE)		Fenofibrate (mean ± SE)	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
N	7	7	7	7	7	7
Male/female	1/6	1/6	2/5	2/5	1/6	1/6
BMI (kg/m^2)	24.8 ± 2.2	23.9 ± 2.3	25.9 ± 1.5	25.1 ± 1.4	25.6 ± 1.9	25.1 ± 2.0
Total cholesterol (mg/dL)	271 ± 45*	262 ± 26*	262 ± 26*	187 ± 32*	251 ± 37*	225 ± 45*
LDL-C (mg/dL)	186 ± 36*	141 ± 35*	174 ± 10*	104 ± 20*	172 ± 32*	140 ± 35*
HDL-C (mg/dL)	59 ± 15	61 ± 12	51 ± 3	56 ± 9	44 ± 14*	60 ± 16*
Triglyceride (mg/dL)	144 ± 77	109 ± 50	189 ± 94*	151 ± 78*	178 ± 95*	123 ± 66*
Fibrinogen (g/dL)	3.65 ± 0.75	4.26 ± 0.74	3.38 ± 0.84	3.39 ± 0.51	3.31 ± 0.60*	3.19 ± 0.62*
Erythrocyte deformability (ms/cell)	3.07 ± 0.16*	2.70 ± 0.26*	2.93 ± 0.22*	2.58 ± 0.12*	3.02 ± 0.15*	2.62 ± 0.14*

* $P < .05$ (pretreatment vs posttreatment).

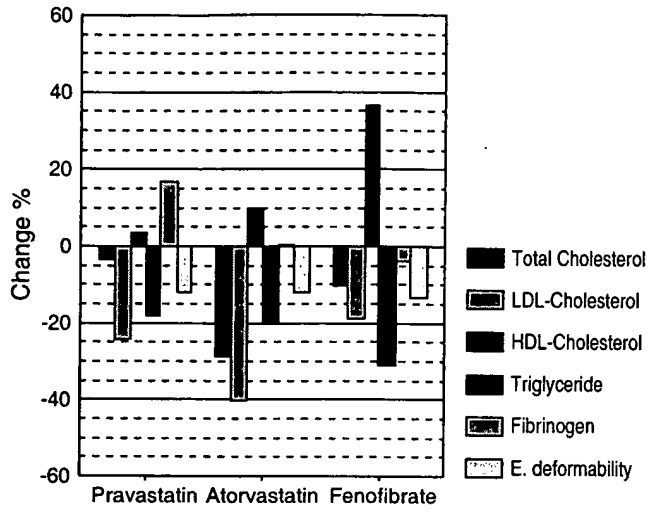

Fig. 1. Change in lipid and hemorheological parameters in all groups during the 8-week treatment period.

difference in BMI, lipid profile, fibrinogen level, and erythrocyte deformability index values among these 3 groups before treatment ($P > .05$).

3.2. Change in lipid parameters

As shown in the Table 1 and Fig. 1, in all groups, there were statistically significant reductions in total cholesterol and LDL-C levels ($P < .05$). The most prominent total cholesterol– and LDL-C–lowering effect (28.6%, 40.2%) was measured after atorvastatin treatment. The triglyceride levels were significantly reduced in atorvastatin (20.1%) and fenofibrate groups (31%) ($P < .05$), but not in pravastatin group (18.2%) ($P > .05$). There was no significant change in HDL-C levels during the treatment with statins (pravastatin [+3.38%] and atorvastatin [+9.8%]; $P > .05$), but there was a significant increase in fenofibrate group (+36.4%) ($P < .05$).

3.3. Change in hemorheological parameters

As shown in Fig. 1, the erythrocyte deformability index was improved in all groups in the posttreatment period ($P < .05$). There was no significant difference in the degree of erythrocyte deformability index improvement among these 3 groups ($P > .05$).

There was no significant change in fibrinogen levels during the treatment of atorvastatin and pravastatin group patients ($P > .05$). However, in fenofibrate group, fibrinogen levels were reduced significantly ($P < .05$).

4. Discussion

Our study revealed that hyperlipidemia treatment improves not only the lipid profile but also the hemorheological parameters.

In agreement with previous studies, patients receiving statin drugs had decreased total cholesterol and LDL-C levels [24]. The most prominent cholesterol-lowering effect was among patients administered atorvastatin [25]. Atorvastatin is a new generation 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitor of which metabolites stay longer in plasma and inhibit HMG-CoA reductase longer than the other statins [26].

Although pravastatin had no significant triglyceride-lowering effect, atorvastatin and fenofibrate had significant triglyceride-lowering effect. Atorvastatin has been shown to inhibit very low density lipoprotein (VLDL) secretion by limiting the availability of free cholesterol or cholesteryl esters for lipoprotein assembly, and it stimulates LDL receptors so the catabolism of VLDL and intermediate density lipoprotein increases. By these mechanisms, HMG-CoA reductase inhibitors lower triglyceride levels [25,26]. Fenofibrate administration significantly lowers both cholesterol and triglyceride levels. However, the most prominent effects with fenofibrate treatment were on triglyceride-lowering and HDL-increasing effects −31% and +36.4%, respectively. It is estimated that both enhanced catabolism of triglyceride-rich particles and reduced secretion of VLDL underlie the hypotriglyceridemic effect of fibrates [27-29]. Fibrates activate specific transcriptional factors belonging to the nuclear receptor superfamily, termed peroxisome proliferator-activated receptors (PPARs) [30]. The PPAR-α form mediates fibrate action on HDL-C levels via transcriptional induction of synthesis of the major HDL apolipoproteins, apoA-I and apoA-II. Previous reports revealed that fibrates increase HDL levels by approximately 15% to 25% [19,28,30]. However, in our study, we found 36.4% increase in HDL levels. These differences may result from the use of a limited number of fenofibrate-treated patients in our study. This finding has to be repeated in studies with greater numbers of patients. Although statins decrease all subtypes of LDL, fibrates mainly do not affect total LDL levels; they rather induce a shift in the LDL subtype distribution [31]. With these mechanisms, fibrates have beneficial effect on coronary artery disease [31].

In all groups, erythrocyte deformability was increased after administration of antihyperlipidemic drugs. In previous preliminary reports, erythrocyte deformability has been shown to increase not only with decreases in plasma cholesterol levels, but also with a decrease in plasma triglyceride levels [10,32-35]. Decrease in plasma cholesterol level was considered to be involved in the improvement of erythrocyte rheological properties by changing erythrocyte membrane phospholipid composition and phosphatidylcholine concentration [10,33,36,37]. Moreover, high plasma triglycerides could modulate the entry of cholesterol into platelets and thus decrease the free cholesterol-phospholipids ratio. The erythrocyte activities of various Na^+ or K^+ transport systems, including the Na^+-K^+ adenosine triphosphatase, the Na^+ leak, the Na^+-K^+ cotransport, and the Na^+-Li^+ countertransport, have also been shown to change with the plasma triglycerides level [12,33,38]. In our study, we could not find any significant difference in improvement of erythrocyte deformability index among patients treated with pravastatin,

atorvastatin, and fenofibrate. However, fenofibrate has an additional beneficial effect on fibrinogen levels that other agents do not have. Serum fibrinogen is directly correlated with plasma viscosity [6], which is also a cardiovascular risk factor [39]. As previously mentioned, fibrates exert their major effects via PPAR-α. Recently, it has been shown that PPAR-α regulates fibrinogen gene expression in rodents [30]. This animal study supports the results of our study. In addition, several previous studies also have shown that fenofibrate decreases fibrinogen in human beings [31,40-42]. Previous studies showed that there was no concensus about the effect of the statin on the fibrinogen levels [15,16]. The difference in results may be related to methodological factors. The immunologic assay is sensitive to fibrinogen as well as to fibrinogen degradation products, and thus may measure a higher value under certain conditions. In our study, the Clauss method that is not affected with the fibrinogen degradation products was used for fibrinogen levels.

5. Conclusion

These data show that these 3 groups of antihyperlipidemic drugs have beneficial effects on erythrocyte deformability index beyond their lipid-lowering effects. In addition, fenofibrate has significant beneficial effect on fibrinogen levels, which is one of the important cardiovascular risk factor.

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